

Synthesis, corticotropin-releasing factor receptor binding affinity, and

pharmacokinetic properties of triazolo-, imidazo-, and pyrrolopyrimidines and -pyridines

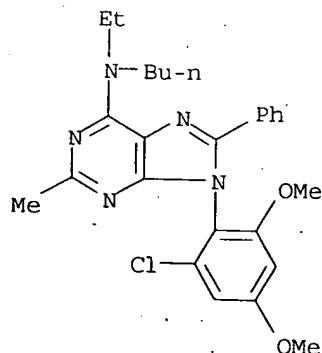
AU Chorvat, Robert J.; Bakthavatchalam, Rajagopal; Beck, James P.; Gilligan, Paul J.; Wilde, Richard G.; Cocuzza, Anthony J.; Hobbs, Frank W.; Cheeseman, Robert S.; Curry, Matthew; Rescinito, Joseph P.; Krenitsky, Paul; Chidester, Dennis; Yarem, Jerry A.; Klaczkiewicz, John D.; Hodge, C. Nicholas; Aldrich, Paul E.; Wasserman, Zelda R.; Fernandez, Christine H.; Zaczek, Robert; Fitzgerald, Lawrence W.; Huang, Shiew-Mei; Shen, Helen L.; Wong, Y. Nancy; Chien, Ben M.; Quon, Check Y.; Arvanitis, Argyrios
 CS Departments of Chemical and Physical Sciences and of Biological Sciences, DuPont Pharmaceuticals Company, Wilmington, DE, 19880-0500, USA
 SO Journal of Medicinal Chemistry (1999), 42(5), 833-848
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 IT 220953-13-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(CRF receptor binding affinity of triazolo-, imidazo-, and pyrrolopyrimidines and -pyridines prepd. from amines, alcs., pyrimidine and pyridine derivs.)

RN 220953-13-9 CAPLUS

CN 9H-Purin-6-amine, N-butyl-9-(2-chloro-4,6-dimethoxyphenyl)-N-ethyl-2-methyl-8-phenyl- (9CI) (CA INDEX NAME)



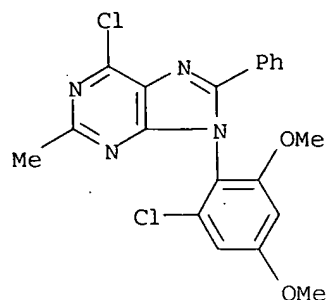
IT 220952-86-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

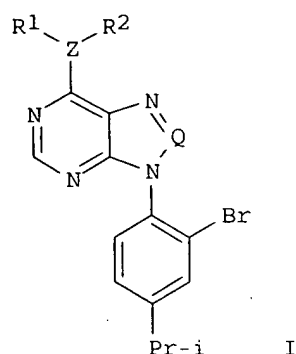
(CRF receptor binding affinity of triazolo-, imidazo-, and pyrrolopyrimidines and -pyridines prepd. from amines, alcs., pyrimidine and pyridine derivs.)

RN 220952-86-3 CAPLUS

CN 9H-Purine, 6-chloro-9-(2-chloro-4,6-dimethoxyphenyl)-2-methyl-8-phenyl- (9CI) (CA INDEX NAME)



GI



I

AB The synthesis and CRF receptor binding affinities of several new series of N-aryltriazolo- and -imidazopyrimidines and -pyridines, e.g., I (R1 = n-Bu, CH₂Et2, CH₂CH₂OH, etc., R2 = Et, H, Me, etc., Q = N, CH, CMe, CCF₃, Z = N, O), are described. These cyclized systems were prepd. from appropriately substituted diaminopyrimidines or -pyridines by nitrous acid, orthoester, or acyl halide treatment. Variations of amino (ether) pendants and arom. substituents have defined the structure-activity relationships of these series and resulted in the identification of a variety of high-affinity agents (K_i's < 10 nM). On the basis of this property and lipophilicity differences, six of these compds. were initially chosen for rat pharmacokinetic (PK) studies. Good oral bioavailability, high plasma levels, and duration of four of these compds. prompted further PK studies in the dog following both i.v. and oral routes of administration. Results from this work indicated I (R1 = R2 = (CH₂)OMe, Q = Z = N; R1 CH₂CH₂OMe, R2 = H, Q = Z = N) had properties believe to be necessary for a potential therapeutic agent, and I (R1 = R2 = (CH₂)OMe, Q = Z = N) has been selected for further pharmacol. studies that will be reported in due course.

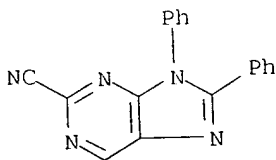
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1997:757616 CAPLUS
DN 128:58662

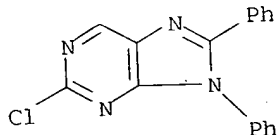
Patel

<6/21/2003>

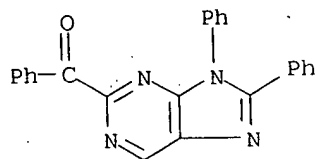
L4 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2003 ACS
 AN 1990:514920 CAPLUS
 DN 113:114920
 TI Purines. IX. Reaction of 9-phenyl-9H-purine-2-carbonitriles with Grignard reagents
 AU Tanji, Kenichi; Higashino, Takeo
 CS Sch. Pharm. Sci., Univ. Shizuoka, Shizuoka, 422, Japan
 SO Heterocycles (1990), 30(1, Spec. Issue), 435-40
 CODEN: HTCYAM; ISSN: 0385-5414
 DT Journal
 LA English
 OS CASREACT 113:114920
 IT 129006-37-7P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. and reaction of, with Grignard reagents)
 RN 129006-37-7 CAPLUS
 CN 9H-Purine-2-carbonitrile, 8,9-diphenyl- (9CI). (CA INDEX NAME)



IT 129006-33-3P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. and reaction of, with cyanide)
 RN 129006-33-3 CAPLUS
 CN 9H-Purine, 2-chloro-8,9-diphenyl- (9CI) (CA INDEX NAME)

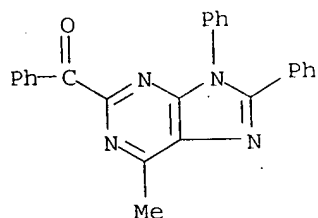


IT 129006-43-5P 129006-44-6P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)
 RN 129006-43-5 CAPLUS
 CN Methanone, (8,9-diphenyl-9H-purin-2-yl)phenyl- (9CI) (CA INDEX NAME)

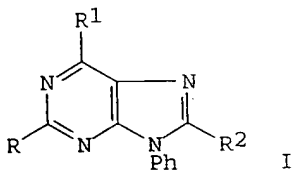


RN 129006-44-6 CAPLUS

CN Methanone, (6-methyl-8,9-diphenyl-9H-purin-2-yl)phenyl- (9CI) (CA INDEX NAME)



GI



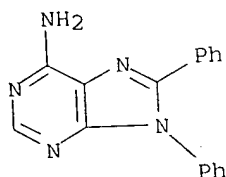
AB The Pd-catalyzed cross-coupling reaction of chlorophenylpurines I (R = Cl, R¹ = H, Me, R² = H, Ph; R = H, Me, R¹ = Cl, R² = H, Ph) with KCN proceeded to give purinecarbonitriles I (R = cyano, R¹ = H, Me, R² = H, Ph; R = H, Me, R¹ = cyano, R² = H, Ph). The conversion of I (R = cyano) into I (R = Ac, COEt, Bz) was achieved by treatment with Grignard reagents.

L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1990:458784 CAPLUS
DN 113:58784
TI Purine derivatives as competitive inhibitors of human erythrocyte membrane
phosphatidylinositol 4-kinase
AU Young, Rodney C.; Jones, Martin; Milliner, Kevin J.; Rana, Kishore K.;
Ward, John G.
CS Smith Kline and French Res. Ltd., Welwyn/Hertfordshire, AL6 9AR, UK
SO Journal of Medicinal Chemistry (1990), 33(8), 2073-80
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 113:58784
IT 127820-25-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and phosphatidylinositol 4-kinase inhibition by)

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<6/21/2003>

RN 127820-25-1 CAPLUS
CN 9H-Purin-6-amine, 8,9-diphenyl- (9C1) (CA INDEX NAME)



AB The possibility of deriving a potent, cell-penetrating inhibitor of human erythrocyte phosphatidylinositol 4-kinase, competitive with respect to ATP, has been investigated in a series of purine derivs. and analogs. The purine nucleus is not essential for binding to the ATP site but offers the advantage of synthetic accessibility to its derivs. The optimum substitution pattern in purine consisted of an electron-releasing substituent in the 6-position (e.g. amino, as in adenine) and a compact, lipophilic group in either the 8-position or, preferably, the 9-position, suggesting the importance of the N-1 lone pair and hydrophobic contributions of the 8- and 9-substituents to binding. The most potent inhibitor synthesized was 9-cyclohexyladenine, which has an apparent K_i value of 3.7 μM .